

What's Inside

Cover Story
ETA Omega-3
A New *Wave*
Sweeps the
Sea
Pg.1

New Supplement Review:
The Rishi's Renewal
Science and the
"Science of Life"
Pg. 10

Breaking Health News
Hot off the press!
Pg. 20

A Cut Above the Rest
Holistic International's and
Jarrow Formulas' hottest
new products.
Pg. 34

The Bigger Picture
"QuickSilverFish"
From *Health*food to *Harm*food?
Pg. 26

I want to know!
We take your most difficult
questions.
Pg. 24

Advanced Orthomolecular Research
4101- 19 St. NE #9
Calgary, AB
Canada T2E 6X8

www.HolisticInternational.com
e-mail: AOR@cadvision.com



Preventative
Alternative
Ayurvedic
Holistic
Naturopathic
Orthomolecular

The Holistic Lifestyle

Volume 1

Issue 7

September 2001



If you – or someone for whom you care – suffer with chronic **inflammation**, then by now you'll have heard of the new "**COX-2 inhibitor**" drugs. The latest painkillers to come out the pharmaceutical industry, COX-2 inhibitors – drugs with names like **celecoxib [Celebrex®]** and **rofecoxib [Vioxx®]** – have become media darlings because they relieve the pain of **rheumatoid arthritis** and other diseases of chronic inflammation, without the risks to the stomach and digestive system that were associated with the older **NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)**, including ibuprofen [Motrin® or Advil®], naproxen [Naprosyn®], indomethacin

[Indocin®]), and the old sawhorse, aspirin).

All of these drugs – as well as the older **steroid drugs**, such as **cortisone** – ultimately work by interrupting the body's production of a class of local cellular "hormones" called **eicosanoids** (eye-KOSS-ah-noids). Eicosanoids are the messengers that cells use to communicate with one another, coordinating their activities. **Some ("bad") eicosanoids promote inflammation, while other ("good") eicosanoids have potent anti-inflammatory functions.** Thus, the body's inflammatory response rests in large part on the balance of "good" and "bad"

Welcome Readers

The Holistic Lifestyle

Volume 1, number 7
September 2001

Executive Editor
Dr. Traj P.S. Nibber

Core Research & Writing
Michael Rae

Graphic Design/Art Production
Danika Challand
Shebodo@hotmail.com

Style & Grammar Editing
Judith Dutton

Holistic International, manufacturers and distributors of the most exciting lines of envelope-pushing nutritional supplements in Canada, welcomes you to this issue of *The Holistic Lifestyle*, published bimonthly. *The Holistic Lifestyle* is designed to provide vital information and news of breakthrough research. By providing clearly-written articles, and the primary sources on which they are based, we hope to help you further your own research, assisting you to make the best supplement and lifestyle choices to meet your unique health goals. *The Holistic Lifestyle* also addresses broader health issues, and the impact of government regulations on your health freedom.

Comments? Questions?
We want to hear from you!

The Holistic Lifestyle
c/o Advanced Orthomolecular Research
4101-19 St NE #9
Calgary, AB
T2E 6X8
1-800-387-0177

holistic@cadvision.com

The content of this newsletter is provided for informational purposes only, and is not intended as medical advice for individuals, which can only be provided by a healthcare professional.

Contents © Holistic International™ and Michael Rae 2001; Design © Danika Challand 2001.



eicosanoids produced by your cells when they hear the immune system's inflammatory call.

Of *Saboteurs* and Janus-Faced COX

When faced with the pain and inflammation of “bad” eicosanoids, one's first instinct might be to follow the example of the old French *saboteurs*. These factory workers, furious that their livelihoods – and sometimes their limbs, or even their lives – were being lost to the new machinery in the Industrial Revolution's factories, would throw their wooden shoes (in French, “*sabots*”) into the offending equipment. The shoes would get stuck in the machines' wooden gears, jamming them, breaking them ... bringing them to a crashing halt.

The NSAID drugs – and especially aspirin – are a lot like those old wooden shoes. The cell's ability to make eicosanoids depends on the functioning of a group of key enzymes. These enzymes work much like the machines on a conveyor belt: enzymes take the materials they're given (**substrates**) and shape them into something new (**products**), before passing them down the line for further processing by other enzymes.

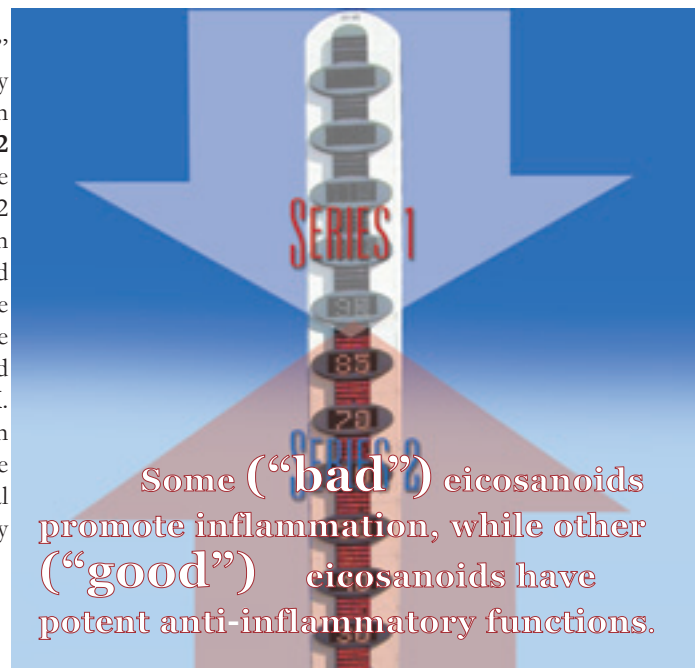
One group of “bad” eicosanoids that are heavily involved in the short-term pain of inflammation is the **series-2 prostanoid** group. Like all the “bad” eicosanoids, series-2 prostanoids are made from an omega-6 fatty acid called **arachidonic acid (AA)**. The enzyme used to make prostanoids out of AA is called **cyclooxygenase, or COX**. Because of COX's role in creating “bad” prostanoids, the giant pharmaceutical conglomerates originally

developed pain-killing drugs using a strategy just like that used by the saboteurs of the Industrial Revolution: they designed the NSAIDs to jam up the works – the more thoroughly, the better.

The problem with this approach is that COX is an enzyme with two faces. While one form of COX (**COX-2**) produces “bad” prostanoids from arachidonic acid, the other form (**COX-1**) produces prostanoids which serve so-called “house-keeping” functions – functions which are vital to health of organs like the stomach and kidneys. So totally shutting down the COX machinery – as is done by first-generation NSAIDs – amounts to a recipe for stomach ulcers and kidney damage.

It's because of the safety issues with the old NSAIDs that the media has hailed the new “COX-2 inhibitor” class of NSAIDs with such enthusiasm. These drugs are a bit more targeted in their design: they strongly block the pro-inflammatory COX-2, but only mildly inhibit the supportive functions of COX-1 alone. As a result, they seem work as well as most NSAIDs at killing pain, but without the stomach ulcer side-effects.

Celebrex® and Vioxx® appear to be no safer for the kidneys than conventional NSAIDs



Some (“bad”) eicosanoids promote inflammation, while other (“good”) eicosanoids have potent anti-inflammatory functions.

ETA Omega-3

A New Wave Sweeps the Sea



ETA is far superior to other **omega-3s** at quenching the fires of **inflammation**

That doesn't mean these drugs are perfect, however. Despite theoretical expectations, Celebrex® and Vioxx® appear to be no safer for the kidneys than the older NSAIDs;¹ as well, the way these drugs are metabolized by the body can cause them to have serious interactions with other drugs.² And there's another reason to be wary of the synthetic COX-2 inhibitors. While they certainly provide symptomatic relief in the short term, **COX-2 inhibitors can actually accelerate the underlying inflammatory disease in the long term.**

The Ticking Timebomb

Drugs that work by only inhibiting COX-2 prevent the formation of the series-2 prostanoids, which are *one* family of "bad" eicosanoids. But there's *another* family of "bad" eicosanoids: the **series-4 leukotrienes**. Like "bad" prostanoids, "bad" leukotrienes are made from arachidonic acid. However, cells use different "machinery" to make leukotrienes: an enzyme called **lipoxygenase (LOX)** enzyme pathway. That is, the body uses two different enzymes to make two different finished products from the same raw material – sort of like starting with pasta dough, but using one machine to make manicotti and another to make ravioli.

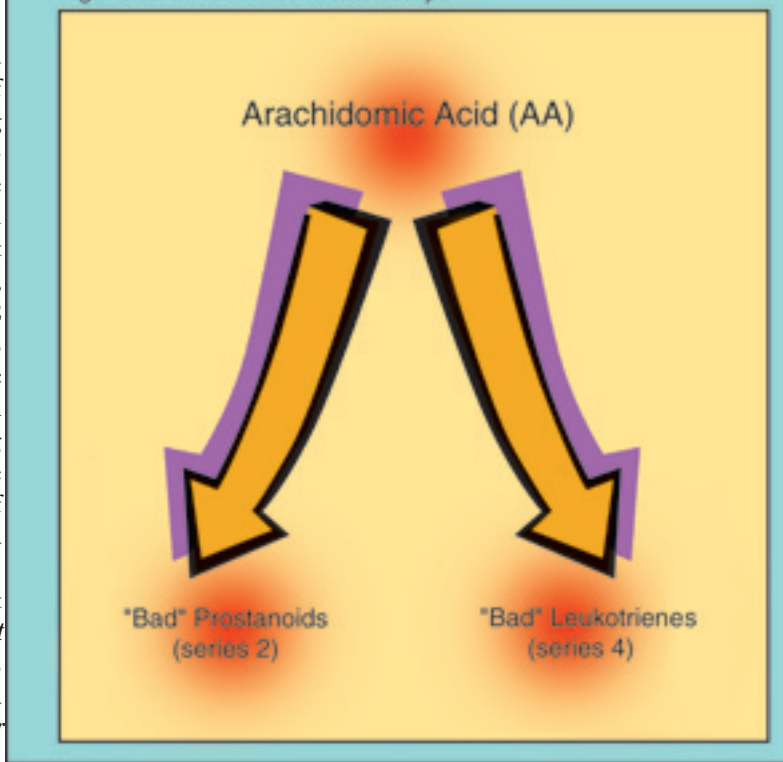
Both the prostanoids (made by COX-2) and the leukotrienes (made by LOX) play important roles in the inflammation process – but in different places, in different ways, and on different time schedules. Prostanoids are usually elevated in the inflamed tissue *itself*, and are more strongly involved in the **short-term** pain of inflammation. In rheumatoid arthritis, for instance, series-2 prostanoids are at work in the thick lubricating material (**synovial fluid**) that bathes the joint. By contrast, **leukotrienes are the eicosanoids released by immune cells involved in the body's inflammatory responses, and are more responsible for the long-term consequences of inflammation, which can result when a deranged immune system attacks the very body which it was designed to defend.**

And that's where you run into danger if you're *only* blocking COX-2. When COX-2 is blocked, the arachidonic acid doesn't just disappear. Instead, **inhibiting COX-2 alone merely puts more arachidonic acid to work in making leukotrienes³⁻⁵** (see **Figure 1**). Think of the flow of water in a river with two arms. If you dam up just one arm, then *that* arm's water levels will run down to a trickle ... but *the other arm's shores will flood.*

This effect has serious ramifications if your inflammation is caused by a dysfunctional immune system, as is the case in **rheumatoid arthritis, in psoriasis, and in most inflammatory**

bowel disease (IBD) cases (including **Chron's disease** and **ulcerative colitis**) and **asthma**. Thus, for instance, even though people suffering with IBD have high levels of prostanoids from COX-2 as part of their disease, the drugs that work by **inhibiting COX exclusively can not only permanently worsen IBD, but can also create an artificial form of the disease,**⁷ reactivate the disease when it had been dormant,⁸ or worsen intestinal permeability ("leaky gut") in otherwise healthy relatives of Chron's victims.⁹ Moreover, evidence exists to suggest that this may apply to new COX-2 inhibitors just as it applied to older NSAID drugs, although the effect is likely to be much milder.¹⁰

Figure 1. The Cox and Lox Pathways



Likewise, there is the phenomenon of **"aspirin-induced asthma,"** seen in about 10-20% of asthma sufferers, in which **COX-inhibiting drugs (including older NSAIDs¹¹ and to some extent the new COX-2 inhibitors^{12,13}) can exacerbate**



existing asthma and trigger flareups – precisely because of increased leukotriene production.⁴

In fact, to say that blocking the COX pathway simply *diverts* the arachi-

donic acid floodwaters into the LOX channels may underestimate the seriousness of the effect. The reason: ironically, despite their role in the *short-term* pain of inflammation, **prostanoids derived from COX-2 may actually help to shield the body from the long-term ravages of leukotrienes!**

For one thing, **some prostanoids directly put the brakes on overproduction of leukotrienes.**^{14,15} On top of this, some prostanoids help **keep tumor necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1) under control.**¹⁹ TNF-alpha and IL-1 are rampaging **cytokines** (a kind of messenger chemical in the immune system) which give the orders that unleash the body's immune cell arsenal. This is great when you have a cold, but disastrous in autoimmune disorders. In rheumatoid arthritis, for instance, **TNF-alpha and IL-1 give the command for immune cells to attack the affected joints,**^{20a} and stimulate the production of **collagenase enzymes** which tear down joint tissue.²¹

Etanercept (Enbrel®), a hot drug for rheumatoid arthritis just approved by Health Canada this March, reduces the pain of the disease, while actually slowing down the long-term joint destruction, *precisely* because it soaks up excess TNF-alpha, preventing it from wreaking its havoc. The cost? Biweekly injections cost the average American user \$12 000 US a year.

But if TNF-alpha gives the orders, it's the leukotrienes that make sure they're carried out. **If TNF-alpha is the general, then leukotrienes are the platoon leaders in the field, and the body's immune cells are the "grunts."**

COX-inhibiting drugs, including the new COX-2 inhibitors, can exacerbate existing asthma and trigger flareups

Because some prostanoids from COX-2 can help to keep a lid on the hazards of leukotrienes, a synthetic version of the **prostanoid PGE1 actually protects joint tissue against damage from these cytokines,**¹⁸ and NSAID **drugs, which block COX-1 as well as COX-2, are known to cause long-term joint damage.**^{22,23}

Does this mean that series-2 prostanoids are "good" after all? Not exactly. But few things in the body serve *exclusively* negative functions: for example, although having too much LDL ("bad") cholesterol in your blood will increase your long-term risk of heart disease, some amount of LDL is needed day-to-day for making the membranes to your cells. So when you block the prostanoids *alone*, you get rid of their directly hurtful effects, but you also lose their *counterbalancing* effects on leukotrienes. **Blocking the COX pathway without also dealing with leukotrienes creates an imbalance – an imbalance which ultimately trades short-term gain for long-term pain.**

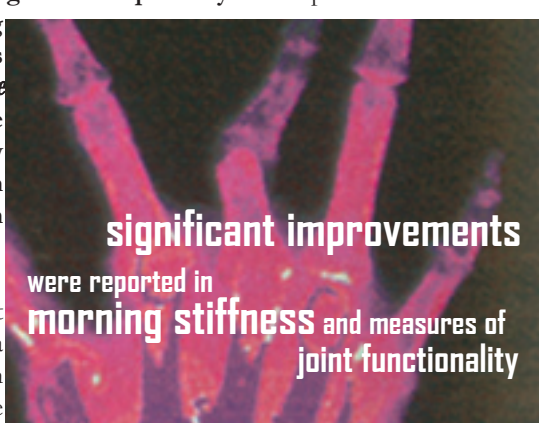
Therefore, we don't just want a supplement which blocks COX: we want a supplement which will defend us against *both* short-term suffering caused by series-2 prostanoids, *and* long-term damage from series-4 leukotrienes. To put it another way: **what people suffering with autoimmune disorders most need is a "dual pathway inhibitor:"²⁴ a molecule which will shut down COX-2 and LOX alike, preventing the formation of all "bad" eicosanoids (see Figure 1).**

That's a pretty hard position to fill. Our dream molecule must be at once

broad-spectrum *and* carefully focused, addressing both immediate suffering and long-term risk. Like NSAIDs, this molecule would inhibit COX-2. Like the COX-2 inhibitors, it would leave the essential housekeeping functions of COX-1 alone. And like the asthma drug zileuton (Zyflo®), it would block the LOX pathway. But unlike *any* of these drugs, our miracle molecule would do all of these things at once, with negligible side-effects.

From the perspective of the medical establishment, this doubtless sounds like a job for some pharmaceutical giant. The transnational drug lords would be delighted to invest in a small army of specialized scientists, a billion-dollar research budget, and a decade of development time, if it were to culminate in a patent-protected, monopoly pharmaceutical with the potential of a true dual-pathway inhibitor.

But Nature has once again beaten the pharmaceutical transnationalss to the finish line. An obscure, hard-to-find omega-3 fatty acid already fits the bill.



Introducing ETA
Eicosatetraenoic acid (ETA) is an omega-3 fatty acid you probably haven't heard much about. Because ETA is so rare in food sources,

there's been little study of its role in the effects of diet on chronic disease – unlike the well-known **eicosapentaenoic acid (EPA)** and **docosahexaenoic acid (DHA)**, which are easily in fatty fish and in regular fish-oil supplements). The rarity of ETA has also meant that it's been hard to make a commercial supplement based on ETA. It's also meant that, until recently, little research had been performed on it in supplement form, as compared with the extensive research on readily-available fish-oil supplements. The rule has been: *you go*

ETA Omega-3

A New Wave Sweeps the Sea

with what you've got.

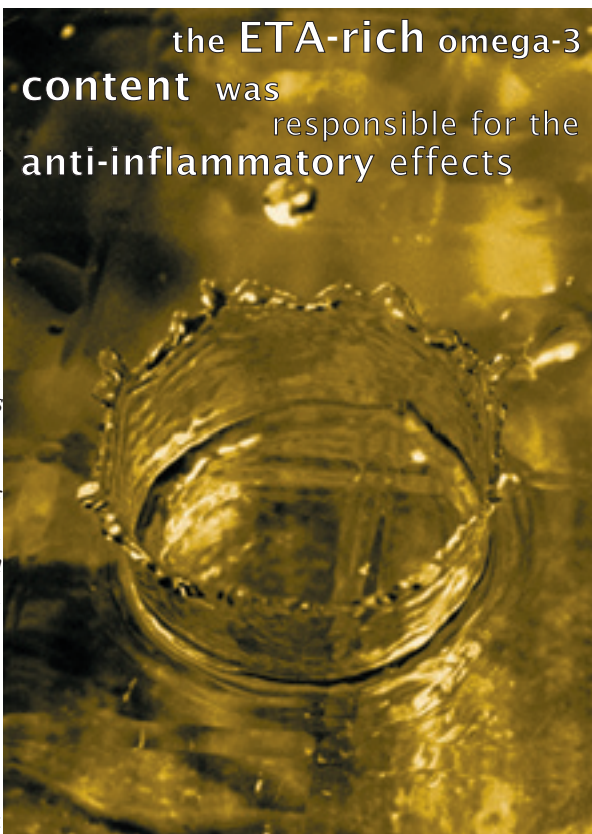
Yet there *has* been research done on ETA in the past—it's just that the researchers didn't know what it was that they were studying. While ETA is very rare in the normal Western diet, it *is* found in significant amounts in the fatty acids of the green-lipped mussel (*Perna canaliculus*), a food used since time immemorial by the coastal Maoris, the aboriginal peoples of New Zealand. And, indeed, statistics show that

those Maoris who live near the shore (whose diet contains a significant amount of green-lipped mussel) have a very low reported incidence of arthritis – whereas their inland cousins, who eat little of this sea-sourced food, have the same rates of arthritis as Europeans living on the islands.²⁵

After first being alerted to the traditional use and some anecdotal evidence, a group of researchers at the Victoria Infirmary in Glasgow, Scotland performed a preliminary, open study of the crude extract of the green-lipped mussel in people with arthritis (55 cases of rheumatoid arthritis and 31 osteoarthritis victims).²⁶ In this study, patients were treated with the crude extract for anywhere from six months to over four years; **over two-thirds of those suffering with rheumatoid arthritis, and over one third of those with osteoarthritis, were reported to benefit from the crude extract.**

Encouraged by their preliminary findings,

the ETA-rich omega-3 content was responsible for the anti-inflammatory effects



Then *all* patients were assigned to receive the active treatment for a further three months.

During the initial, placebo-controlled phase, **59% of the people with rheumatoid arthritis improved while receiving the crude extract**, compared with only 27% of the people receiving the dummy pill; and **in the osteoarthritis group, 37.5% of people receiving the crude extract improved, versus only 13.6% of the fish-pill stand-ins.**

But when other investigators tried to confirm the results of this study, the results were contradictory. While the effectiveness of the crude extract was confirmed by French investigators in a double-blind, placebo-controlled trial,²⁸ two *other* such trials using the crude extract reported that it had no effect.^{29,30} The same contradictions turned up in animal experiments.³¹⁻³⁵ What was going on?

these scientists initiated a placebo-controlled, double-blind, study.²⁷ Sixty-six patients on a waiting list for joint surgery at the Infirmary (28 rheumatoid arthritis sufferers and 38 people with osteoarthritis), who did not have an allergy to fish or shellfish, were randomly placed into one of two groups, receiving either 1050 mg of the crude extract of *Perna canaliculus* or the same amount of an inactive fish preparation.

The Missing Ingredient

For a decade or so, the contradictory results led most scientists to conclude that the green-lipped mussel was a dead end for research, and virtually no new work was done. Then, in 1995, scientists at Australia's Royal Melbourne Institute of Technology resolved the contradiction in the previous studies, providing the key that explained the inconsistent results of previous studies. These researchers hypothesized that the anti-inflammatory properties of the green-lipped mussel were most likely due to some specific ingredient, which might have been present in some crude extracts and not in others.

Studies performed by this group proved the hypothesis correct. Specifically, **it was the free fatty acids – and, in particular, the ETA-rich omega-3 content – which was responsible for the anti-inflammatory effects of *Perna canaliculus*.**³⁶⁻³⁹ Tellingly, a test which compared seven commercially-available crude green mussel products with the a stable fatty extract rich in ETA revealed strong anti-inflammatory powers in the ETA extract, while the crude extracts were found to vary wildly in strength.³⁸ More tellingly, when the inflammation-fighting powers of a stable ETA-rich extract were compared with crude *P. canaliculus* extracts whose fatty acid content had been deliberately removed, the fatty acid extract of the mussel exhibited potent anti-inflammatory effects, while the ETA-depleted preparation was found to be completely ineffective.³⁹ And studies using highly purified subfractions of the fatty acid extract demonstrated **that by far the most potent fraction of the fatty acid extract was not the portion with the common omega-3s (EPA and DHA), but the fraction rich in ETA.**^{36,37}

Now the reason for the controversy over green-lipped mussel extracts began to make sense. The crude extracts were not created in a way which would consistently deliver a rich dose of ETA. The products used in these studies did not contain a defined quantity of free fatty acids, nor was the



extract processed or stabilized with the care required to protect what ETA was present in the material. Thus, “The mussel powder used in the original trial was freshly prepared for [the investigators] along with the fish-based placebo. Stability ... may well have been a problem with the material used in [unsuccessful] studies.”⁴⁰ The contradictory results, then, were not the fault of the various research groups, but were almost certainly caused by batch-to-batch variations in the ETA content of crude extracts.

ETA Beats Out the Other Omega-3s

Once we see that the anti-inflammatory powers of the green-lipped mussel were due to its unique, ETA-rich blend of fatty acids, the next logical question is: how does ETA stack up in comparison to other omega-3 sources, such as fish oils and flaxseed oil? Two direct comparison studies have been performed to answer this question, weighing the anti-inflammatory effects of the ETA-rich oil of *P. canaliculus* against those of salmon, cod liver, flaxseed, and two mixed fish oils.^{39,41}

In these studies, the powers of the various omega-3 supplements were tested in animals who were given an inflammation-inducing substance – the same sort of test which had given such contradictory results in tests on the crude green mussel extracts of the previous generation. The various omega-3 supplements (and some other products) were tested by looking at the amount of swelling in the wrist and digits, as

well as through the use of a standardized “arthritis” score, looking at things like how sensitive the animals’ feet were to handling, how thoroughly the animals groomed their inflamed paws, and how mobile the animals were.

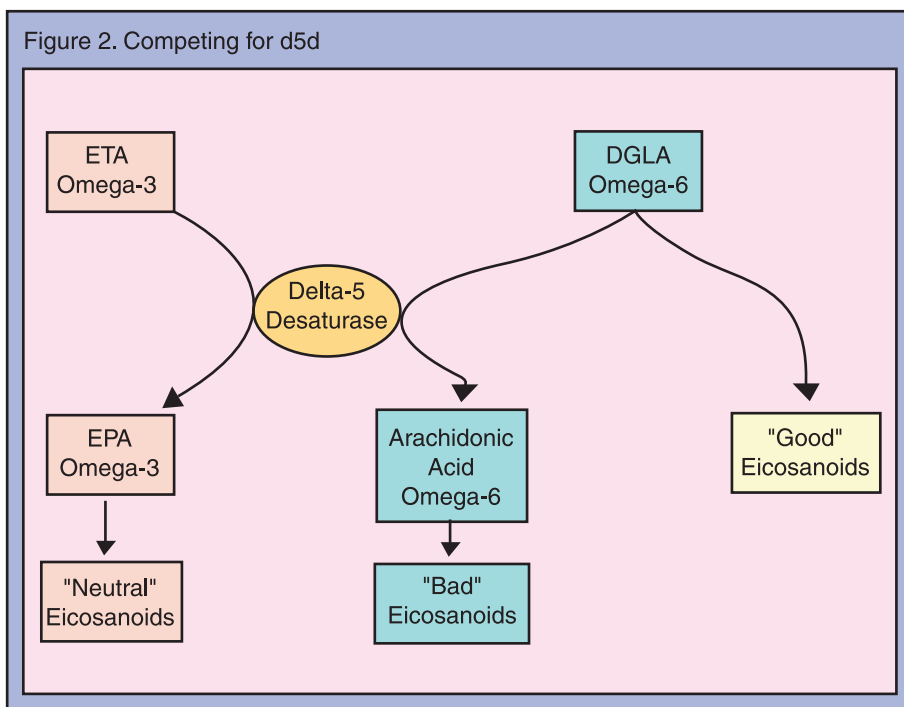
These studies clearly show that the ETA-rich fatty acid extract of *P. canaliculus* is far superior to other omega-3 sources at

quenching the fires of inflammation, giving more potent anti-inflammatory benefits at significantly lower doses. Using the series of tests discussed above, **ETA supplementation lowered arthritis scores by 42³⁹ to 75⁴⁰%, vs. 0 to 31% using conventional omega-3 sources.** Likewise, **rear paw swelling was reduced by 96-98% by the ETA-rich oil, while swelling**

A New Human Trial

With the new understanding that the fragile fatty acid component of the green-lipped mussel was the key to its inflammation-cooling abilities, the lipid extract was put to the real test: a new randomized, double-blind, controlled trial, following essentially the same design as the original controlled study, but using 30 patients in each group

Figure 2. Competing for d5d



was only lowered by 7 to 38% with common omega-3s! These results are all the more remarkable because the dose of ETA-rich *P. canaliculus* oil was only about 1% of that used for the standard omega-3 oils.

Several studies have also compared the ETA omega-3 supplement to drugs used to fight pain and inflammation – the NSAIDs ibuprofen,³⁸ naproxen,³⁸ and indomethacin,^{38,39} two new drugs which work by inhibiting the action of leukotrienes.⁴¹ Remarkably, **ETA performed similarly to, or better than, any of these pharmaceuticals** in inhibiting inflammation and in arthritis scoring.

(rheumatoid or osteoarthritis sufferers) and with modifications approved by the West Ethical committee.⁴⁰ The results: among rheumatoid arthritis sufferers taking the *P. canaliculus* oil, significant improvements were reported in morning stiffness and measures of joint functionality during the double-blinded phase; further, night pain was “much improved” in 40% of subjects, and vanished in an additional 26.7%. Improvements were also seen in some patients’ grip strength and overall visual-scale pain scores, but these results were not found statistically meaningful. Assessment by doctors and patients concluded that **73% of the persons with rheumatoid arthritis had experienced a good response – including 20% who became completely symptom-free** by

ETA Omega-3

A New Wave Sweeps the Sea

the end of the double-blind phase.

The results were similar in the osteoarthritis victims, with significant improvements in morning stiffness and measures of joint functionality reported for the patient group which had taken the *P. canaliculus* oil supplement, though grip strength was not significantly improved. With surprising consistency, 40% of OA patients taking the green-lipped mussel oil supplement saw their night pains improve considerably, including total disappearances in 26.7%. Doctor/patient assessments again judged 73% of people with osteoarthritis to have been improved, though none were symptom-free. No side-effects were seen except for mild water-retention in some patients.

Similar results have been reported in an unpublished pilot trial⁴² and in case reports.⁴³

Breathe Easy

A supplement which blocks both the COX and the LOX pathways would also be a godsend for people who suffer with asthma. In an unpublished double-blind, placebo-controlled study,⁴⁴ asthma sufferers who took the stable oil of *P. canaliculus* experienced significant reductions in the frequency of chest tightness and night waking, cut down on their use of beta-agonist drugs, and saw improvements in their peak airflow. No improvements were seen in the placebo group.

A report in the *Medical Journal of Australia*⁴⁵ supports this finding. It details the case of a 69-year-old patient suffering with both osteoarthritis and asthma. This woman – who was originally taking 100 milligrams of the stable *P. canaliculus* oil daily for her osteoarthritis – found that the supplement also dramatically improved her asthma: using the ETA-rich oil led to an 80% cut in the use of the steroid drug

prednisone, and an increase in peak airflow from 250 liters per minute to 350 over the course of two years.

Sufferers need a “dual pathway inhibitor:” a molecule which will shut down COX-2 and LOX alike

Stopping the Monthly Rollercoaster?

Many women taking stable fatty acid extracts of *P. canaliculus* oil for their arthritis, have also reported that they experience relief from their premenstrual syndrome (PMS) symptoms.⁴¹ This makes sense: the extreme contractions of the uterus which underlie much of the cramping of PMS are ultimately caused by wild hormonal tides, but the increase in contraction is largely delivered through “bad” eicosanoid signals – eicosanoids from both the COX and the LOX pathways.⁴⁶ Furthermore, “bad” eicosanoids actually heighten the pain sensitivity of the uterus, increasing the suffering associated with the physical contractions.⁴⁶

In a recent study,⁴¹ female lab animals were administered the key women’s hormones estrogen, progesterone, and oxytocin in a way that mimics the normal monthly menstrual cycle, and given either the ETA-rich green-lipped mussel oil or an olive oil dummy supplement. Scientists then examined the force and frequency of their isolated uterus’ contractions as a model of menstrual cramping.

While a single treatment with the *P. canaliculus* oil had no effect on uterine contractions, giving the animals the ETA-rich oil for three consecutive days reduced the

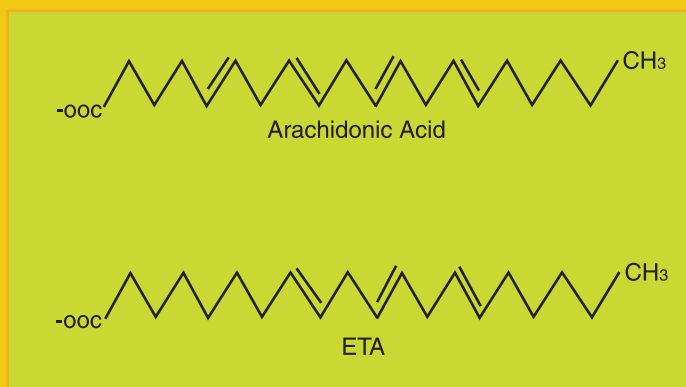
cramping of the uterus when stimulated by the hormone oxytocin. The olive oil treatment had no effect.

How Does It Work?

The answer to this question is a little bit technical. To fully explain the effects of ETA on inflammation, and its superiority to common omega-3 supplements, in a way that’s clear to any intelligent person with no background in the biochemistry, would occupy more space than is available for this article as a whole – and we’ve already had to skim quickly through results which deserve much more detailed reporting. So it’ll take bit more effort to understand this section. Read it carefully if you’re interested – or skip it if you’re not. There won’t be a quiz.

The fact is that all omega-3s have some degree of “dual pathway inhibitor” action, blocking both the short-term pain and inflammation of the prostanooids (from COX-2) and the longer-term immune attacks which are the danger of the leukotrienes (from LOX). These abilities are based on several aspects of the body’s processing of fatty acids. For one thing, the same COX and LOX enzymes which make “bad” eicosanoids from arachidonic acid, can make “neutral” eicosanoids from specific omega-3s. Omega-3s can thus put the brakes on inflammation by tying up the enzymes which would otherwise be put to work making “bad” eicosanoids – thereby

Figure 3. Arachidonic Acid vs. ETA





preventing those eicosanoids from being formed.⁴⁷

Furthermore, like other omega-3s, **ETA is a natural COX-2 inhibitor**, which ties up the inflammatory form of the enzyme without affecting the “housekeeping” function of COX-1.⁴⁸ Remarkably, omega-3s accomplish this feat not *only* by binding up COX-2, but *also* by **actually working at the gene level to reduce the production of COX-2** from the DNA code.⁴⁸ And, at the same time, omega-3s like **ETA also block the formation of leukotrienes⁴⁷ and of TNF-alpha and IL-1 from being produced in the first place⁹** (unlike Enbrel,[®] which works *after the fact* as a TNF “sponge”), cutting levels of these cytokines by as much as **90%⁴⁷** – and again, by working right down at the gene level.⁴⁸

Omega-3s such as ETA also work their magic one step further up the chain, by **reducing the body’s formation of arachidonic acid in the first place.** This effect, again, is the result of tying up an enzyme – in this case, the enzyme which the body uses to *make* arachidonic acid (an enzyme called **delta-5-desaturase (d5d)**). Remember that, when it comes to eicosanoids, **arachidonic acid is the “root of all evil:”** all “bad” eicosanoids – both the series-2 prostanoids and the series-4 leukotrienes – are formed from this omega-6 fatty acid. Every molecule of arachidonic can be used to make a “bad” eicosanoid ... and thus, every AA molecule not made is a potential “bad” eicosanoid nipped in the bud.

So if all omega-3s have these effects, why is it that ETA works so much better than its more common cousins? Simply put, **ETA does a better job than other omega-3s of binding up the key enzymes involved in making “bad” eicosanoids.**

At this point matters become even more complicated, so you’re forgiven if your eyes start to glaze over. One key point is **ETA is an alternative “substrate” for delta-5 desaturase, the enzyme that also makes**

arachidonic acid: that is, ETA is a *raw material*, from which d5d can make a *product*.

If you feed d5d the omega-6 fatty acid **dihommo gamma-linolenic acid (DGLA)**, it will churn out arachidonic acid. From arachidonic acid come the “bad” eicosanoids. But **if you instead feed ETA to d5d, it will make EPA**, the omega-3 found in common fish oil products (see **Figure 2**). And as long as d5d is busy making EPA, it can’t make arachidonic acid. It can’t take on both jobs at the same time.

Though it’s not immediately obvious, this series of relationships actually explains why ETA can tie up d5d more powerfully than can EPA, and thus more effectively prevent the production of arachidonic acid. That’s because **enzymes always bind more strongly to their substrates than to their products.** So while both EPA and ETA can inhibit the arachidonic acid-producing activity of d5d, ETA has the edge, delivering a much stronger effect.

And that edge yields double dividends. Not *only* does keeping arachidonic acid under control prevent the formation of “bad” eicosanoids ... it also leaves the cell with extra DGLA, which can then go on to make “good” eicosanoids, which have potent anti-inflammatory effects (see **Figure 2**). As a result, **ETA-based supplements are believed to actually increase production of “good” eicosanoids from DGLA.**⁵⁰ On top of this, substances made directly from DGLA also inhibit the ability of COX and LOX machinery to make “bad” eicosanoids.^{51,52} It’s a virtuous circle, with the end result being that **the more thoroughly you bind up d5d, the**

more you will inhibit “bad” eicosanoids ... and the more you will support the formation of “good” ones.

Another factor in ETA’s unique anti-inflammatory power is the fact that its chemical structure is so close to that of arachidonic acid (see **Figure 3**). Scientists believe that this similarity may allow ETA to “fool” the LOX enzyme into thinking that it *is* arachidonic acid, thereby again

ETA does a better job than other omega-3s of binding up the key enzymes involved in

outdoing other omega-3s in keeping the inflammatory enzymes safely occupied, instead of busily making “bad” eicosanoids from arachidonic acid itself.^{36,37} Certainly, studies in human immune cells consistently show that ***Perna canaliculus* ETA-rich oil potently blocks formation of “bad” eicosanoids by both LOX^{39,37,53} and COX.³⁹**

Knowing It ... and Living It

In the end, what matters to users of ETA-based omega-3 supplements is not learning technical terms from biochemistry, or understanding the fascinating underlying enzymology. What matters is relief from suffering, and restored functionality. **ETA-based omega-3 supplements deliver what no other natural supplement can: an orthomolecular substance, naturally present in the body and required for its health, which provides powerful support against inflammation in a way that other**

The Bottom Line

- NSAID drugs like aspirin and ibuprofen work by tying up an enzyme which makes a family of microhormones called **prostanoids**.
- The main **side-effects of NSAID drugs** are created because they keep the body from making both “good” and “bad” prostanoids.
- The new **“COX-2” inhibitor drugs have fewer side-effects**, because they don’t interfere with “good” prostanoids.
- However, **COX-2 inhibitors may create long-term problems** by increasing the formation of another class of joint-damaging microhormones called **leukotrienes**.
- Omega-3 fatty acids, such as the EPA and DHA in **common fish oils, can reduce the formation of both “bad” prostanoids and leukotrienes.**
- Studies show that **ETA, a rare omega-3 fatty acid, has much greater anti-inflammatory powers than conventional fish oils.**

ETA Omega-3

A New Wave Sweeps the Sea

natural supplements can't match. In short: the biochemistry **explains** the results seen in animal studies and clinical trials. But only you can **experience** them ... for yourself.

References

1. Brater DC, Harris C, Redfern JS, Gertz BJ. Renal effects of *cox-2*-selective inhibitors. *Am J Nephrol*. 2001 Jan-Feb;21(1):1-15.
2. Fung HB, Kirschenbaum HL. Selective cyclooxygenase-2 inhibitors for the treatment of arthritis. *Clin Ther*. 1999 Jul;21(7):1131-57.
3. Sugaya K, Uz T, Kumar V, Manev H. New anti-inflammatory treatment strategy in Alzheimer's disease. *Jpn J Pharmacol*. 2000 Feb;82(2):85-94.
4. Babu KS, Salvi SS. Aspirin and asthma. *Chest*. 2000 Nov;118(5):1470-6.
5. Wardle TD, Hall L, Turnberg LA. Interrelationships between inflammatory mediators released from colonic mucosa in ulcerative colitis and their effects on colonic secretion. *Gut*. 1993 Apr;34(4):503-8.
6. Hovde O, Farup PG. NSAID-induced irreversible exacerbation of ulcerative colitis. *J Clin Gastroenterol*. 1992 Sep;15(2):160-1.
7. Kirsch M. Drug-induced ileal disease: a new entity in the differential diagnosis of Crohn's disease. *South Med J*. 1994 Apr;87(4):546-8.
8. Dichi I, Dichi JB, Frenhane P, Rodrigues MA, Burini RC, Victoria CR. Reactivation of ulcerative rectocolitis with the use of non-steroidal anti-inflammatory drugs. *Arq Gastroenterol*. 1995 Oct-Dec;32(4):172-7.
9. Zamora SA, Hilsden RJ, Meddings JB, Butzner JD, Scott RB, Sutherland LR. Intestinal permeability before and after ibuprofen in families of children with Crohn's disease. *Can J Gastroenterol*. 1999 Jan-Feb;13(1):31-6.
10. McCartney SA, Mitchell JA, Fairclough PD, Farthing MJ, Warner TD. Selective COX-2 inhibitors and human inflammatory bowel disease. *Aliment Pharmacol Ther*. 1999 Aug;13(8):1115-7.
11. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol*. 1999 Jul;104(1): 5-13.
12. Kosnik M, Music E, Matjaz F, Suskovic S. Relative safety of meloxicam in NSAID-intolerant patients. *Allergy*. 1998 Dec;53(12):1231-3. Cited by (4).
13. Bianco S, Robuschi M, Petrigni G, Scuri M, Pieroni MG, Refini RM, Vaghi A, Sestini PS. Efficacy and tolerability of nimesulide in asthmatic patients intolerant to aspirin. *Drugs*. 1993;46 Suppl 1:115-20.
14. Christman BW, Christman JW, Dworski R, Blair IA, Prakash C. Prostaglandin E2 limits arachidonic acid availability and inhibits leukotriene B4 synthesis in rat alveolar macrophages by a nonphospholipase A2 mechanism. *J Immunol*. 1993 Aug 15;151(4):2096-104.
15. Klockmann MT, Jahn HU, Hippenstiel S, Kramer HJ, Suttrop N. Interaction of human neutrophils with airway epithelial cells: reduction of leukotriene B4 generation by epithelial cell derived prostaglandin E2. *J Cell Physiol*. 1998 Jun;175(3):268-75.
16. Kunkel SL, Chensue SW, Phan SH. Prostaglandins as endogenous mediators of interleukin 1 production. *J Immunol*. 1986 Jan;136(1):186-92.
17. 2: Kunkel SL, Chensue SW. Arachidonic acid metabolites regulate interleukin-1 production. *Biochem Biophys Res Commun*. 1985 Apr 30;128(2):892-7.
18. Dingle JT, Shield MJ. The interactions of cytokines, NSAIDs and prostaglandins in cartilage destruction and repair. *Adv Prostaglandin Thromboxane Leukot Res*. 1991;21B:955-66.
19. Di Battista JA, Martel-Pelletier J, Pelletier J. Suppression of tumor necrosis factor (TNF-alpha) gene expression by prostaglandin E(2). Role Of early growth response protein-1 (Egr-1). *Osteoarthritis Cartilage*. 1999 Jul;7(4):395-8.
20. Moilanen E. Prostanoids and leukotrienes in rheumatoid synovitis. *Pharmacol Toxicol*. 1994;75 Suppl 2:4-8.
- 20a. Hamilton K, Clair EW. Tumour necrosis factor-alpha blockade: a new era for effective management of rheumatoid arthritis. *Expert Opin Pharmacother*. 2000 Jul;1(5):1041-52.
21. Arend WP, Dayer JM. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor alpha in rheumatoid arthritis. *Arthritis Rheum*. 1995 Feb;38(2):151-60.
22. Rashad S, Revell P, Hemingway A, Low F, Rainsford K, Walker F. Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet*. 1989 Sep 2;2(8662):519-22. PMID: 2570233 [PubMed - indexed for]
23. Ronningen H, Langeland N. Indomethacin treatment in osteoarthritis of the hip joint. Does the treatment interfere with the natural course of the disease? *Acta Orthop Scand*. 1979 Apr;50(2):169-74.
24. Lauritsen K, Laursen LS, Kjeldsen J, Bukhave K, Rask-Madsen J. Inhibition of eicosanoid synthesis and potential therapeutic benefits of 'dual pathway inhibition'. *Pharmacol Toxicol*. 1994;75 Suppl 2:9-13.
25. Halpern GM. Anti-inflammatory effects of a stabilized lipid extract of Perna canaliculus (Lyprinol). *Allerg Immunol (Paris)*. 2000 Sep;32(7):272-8.
26. The design and results of this pilot trial were reported in (27).
27. Gibson RG, Gibson SL, Conway V, Chappell D. Perna canaliculus in the treatment of arthritis. *Practitioner*. 1980 Sep;224(1347):955-60.
28. Audeval B, Bouchacourt P. Double blind, placebo-controlled study of the mussel Perna canaliculus in gonarthrosis. *Gaz Medicale*. 1986;93(38):111-6.
29. Huskisson EC, Scott J, Bryans R. Seaton is ineffective in rheumatoid arthritis. *Br Med J (Clin Res Ed)*. 1981 Apr 25;282(6273):1358-9.
30. Larkin JG, Capell HA, Sturrock RD. Seaton in rheumatoid arthritis: a six-month placebo-controlled study. *Ann Rheum Dis*. 1985 Mar;44(3):199-201.
31. Rainsford KD, Whitehouse MW. Gastroprotective and anti-inflammatory properties of green lipped mussel (Perna canaliculus) preparation. *Arzneimittelforschung*. 1980;30(12):2128-32.
32. Couch RA, Ormrod DJ, Miller TE, Watkins WB. Anti-inflammatory activity in fractionated extracts of the green-lipped mussel. *N Z Med J*. 1982 Nov 24;95(720):803-6.
33. Palmer DG. Anti-inflammatory effects of mussel extracts. *N Z Med J*. 1980 Oct 22;92(670):328.
34. Cullen JC, Flint MH, Leider J. The effect of dried mussel extract on an induced polyarthritis in rats. *N Z Med J*. 1975 Mar 12;81(535):260-1.
35. Miller TE, Ormrod D. The anti-inflammatory activity of Perna canaliculus (NZ green lipped mussel). *N Z Med J*. 1980 Sep 10;92(667):187-93.
36. Macrides TA, Kalafatis N. *Int Patent PCT/AU 95/004/85 (1995)*.
37. Macrides TA, Treschow AP, Kalafatis N, Wright PF, Wynne PM. The anti-inflammatory effects of n-3 tetraenoic fatty acids isolated from a lipid extract from the mussel, Perna canaliculus. *Prostaglandins Leukot Essent Fatty Acids*. 1997 Aug;57(2):205(W20).
38. Whitehouse MW, Roberts MS, Brooks PM. Over the counter (OTC) oral remedies for arthritis and rheumatism: how effective are they? *Inflammopharmacol*. 1999;7(2): 89-105.
39. Whitehouse MW, Macrides TA, Kalafatis N, Betts W, Haynes DR, Broadbent J. Anti-inflammatory activity of a lipid fraction (Lyprinol) from the NZ green-lipped mussel. *Inflammopharmacol*. 1997;5(3):237-46.
40. Gibson SL, Gibson RG. The treatment of arthritis with a lipid extract of Perna canaliculus: a randomized trial. *Compl Ther Med*. 1998;6:122-6.
41. Shiels IA, Whitehouse MW. Lyprinol: anti-inflammatory and uterine-relaxant activities in rats, with special reference to a model for dysmenorrhoea. *Allerg Immunol (Paris)*. 2000 Sep;32(7):279-83.
42. Nertz, N. The effect of a stabilized oil (Lyprinol) from green lipped mussel (Perna canaliculus) on pain and Activities of Daily 43. Gibson SL. The effect of a lipid extract of the New Zealand green-lipped mussel in three cases of arthritis. *J Altern Compl Med*. 2000 Aug;6(4):351-4.
44. Yemelyanov A. Report of a clinical trial with Lyprinol in bronchial asthma. Pavlov's St. Petersburg Medical University; unpublished.
45. Harbison SJ, Whitehouse MW. Possible steroid-sparing effect in asthma of lyprinol, a shellfish lipid extract. *Med J Aust*. 2000 Nov 20;173(10):560.
46. Benedetto C. Eicosanoids in primary dysmenorrhoea, endometriosis and menstrual migraine. *Gynecol Endocrinol*. 1989;3(1):71-94.
47. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*. 2000 Jan;71(1 Suppl):343S-8S.
48. Curtis CL, Hughes CE, Flannery CR, Little CB, Harwood JL, Caterson B. n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. *J Biol Chem*. 2000 Jan 14;275(2):721-4.
49. Caughey GE, Mantziaris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr*. 1996 Jan;63(1):116-22.
50. Darlington LG, Stone TW. Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. *Br J Nutr*. 2001 Mar;85(3):251-69.
51. Iversen L, Fogh K, Kragballe K. Effect of dihomogammalinolenic acid and its 15-lipoxygenase metabolite on eicosanoid metabolism by human mononuclear leukocytes in vitro: selective inhibition of the 5-lipoxygenase pathway. *Arch Dermatol Res*. 1992;284(4):222-6.
52. Johnson MM, Swan DD, Surette ME, Stegner J, Chilton T, Fonteh AN, Chilton FH. Dietary supplementation with gamma-linolenic acid alters fatty acid content and eicosanoid production in healthy humans. *J Nutr*. 1997 Aug;127(8):1435-44.
53. Dugas B. Lyprinol inhibits LTB4 production by human monocytes. *Allerg Immunol (Paris)*. 2000 Sep;32(7):284-9.